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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/562,478	KOSUTIC ET AL.
	Examiner	Art Unit
	SAMUEL LIU	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/9/11 & 6/8/11*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1-3 are pending

The amendment filed 6/8/11 which amends claims 1-3 has been entered. Claims 4-13 were cancelled by the amendment filed 12/2/05. Claims 1-3 are under examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 6/8/11 has been entered.

New-Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement; this is a new matter rejection. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of "... about 20 μg/kg at least once a day", which as amended into the claims 1-3 on 5/9/11, is not supported in the specification as originally filed. Applicant can either cancel the new matter or point out specification support for the phrase in the specification as originally filed.

It is of note that the specification does not describe "20 μg/kg at least once a day"; the specification only discloses oral administration of calcitonin oligomer drug of a dose 20 μg/kg

twice a day; wherein said "at least once" (including one, two, three or four time etc.) a day has broader breath than that of the "at least once" a day; and thus, the claim amendment broadens the scope of the claims. Therefore, it is a new matter.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Rejection under 35 U.S.C 102(e), Patent Application Publication or Patent to Another with Earlier Filing Date, in view of the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

CLAIM INTERPRETATION: the limitation "about 20 μg/kg at least once a day", as amended on 5/9/1, (set forth no upper limit for "how many times a day" due to "at least once") is broadly but reasonably interpreted as unlimited amount (as along as reasonable amount) of said dose per day. Thus, the following rejection is applicable.

[1] Claims 1-3 remain rejected under 35 U.S.C. 102(e) as anticipated by Soltero et al. (US 6770625 B2), wherein the fact of intense pain in bone disorder Paget's disease is evidenced by the Yamamoto et al. (US 5059587) (see col. 1, lines 64-65).

In patent claim 62, Soltero et al. teach a method of treating a bone disorder such as "Paget's disease" (see col. 39, lines 56). The method comprises orally administering to a subject in need a pharmaceutical composition comprising "calcitonin (CT)-drug-oligomer conjugate"; wherein CT is salmon calcitonin (patent claim 120-122) and wherein the conjugate is in a mono-dispersed mixture (patent claims 62, 76-79 and 81). Said "oligomer" preferably is "polyethylene glycol" (PEG) (see patent claim 80, and col. 24, lines 27, 35 and 36) linked to Lys^{11} and Lys^{18} residues of calcitonin (patent claim 79). Because intense pain is associated with "Paget's disease", treating said disease would necessarily lead to treatment of the bone pain, a peripheral pain. Since salmon calcitonin (sCT) is unique, the sCT polypeptide inherently reads on instant SEQ ID NO:1. Soltero et al. teaches that dosages can be determined with routine pharmacological procedures known to those skilled in the art, and teaches that the dosage in general is about 0.1 mg/kg (see col.39, lines 28-31). Since instant limitation "...amount is about 20 μg/kg at least once a day" (in claims 1-3) sets forth no upper limit of the amount per day ("at least once" allows for plurality of times of sCT' administration), and since dosages can be determined in accordance with routine pharmacological procedures known to those skilled in the art (Col.39, lines 28-30, Solteron et al.), the Soltero's teaching as to the dosage meets the instant limitation. Thus, claim 1 is anticipated.

Soltero et al. teach the structure: "Salmon calcitonin-$[CO\text{-}(CH_2)_7\text{-}(OC_2H_4O)_7CH_3]_2$" (see col. 31, lines 3-8) wherein "$\text{-}(OC_2H_4O)_7$" is PEG moiety subunits (see col. 25, lines 7-16, this meets the limitation 7 polyethylene glycol subunits), wherein the portion "$CO\text{-}(CH_2)_7$-" is a lipophilic moiety that preferably is a fatty acid moiety (see col. 25, lines 37-40), and wherein "**2**" in outside parentheses "[ ]" indicates that two residues of sCT peptide, i.e., Lys^{11} and Lys^{18}, are

conjugated to the PEG moieties. This teaches the structural limitation of the "conjugate" of claim 3.

Soltero et al. teach that **a** (one) hydrolyzable bond between drug peptide and the "oligomer" (see col. 33, lines 47-50). In accordance with the claim 38 disclosure that PEG is coupled to the "oligomer" (i.e., calcitonin) via Lys^{11} and Lys^{18} residues of calcitonin, thus, one of these two ε-lysine amino groups is conjugated to the PEG through said "hydrolyzable bond" while the other remains non-hydrolysable. This meets the structure of claim 2 "conjugate". Therefore, Soltero et al. inherently teach the method of claim 2.

The applicants' response to the above 102(e) rejection

At pages 3 and 4, the response filed 5/9/11the amendment of claim1 to include the limitation of treating peripheral pain in a subject with the composition (comprising the calcitonin oligomer conjugate) of about 20 μg/kg at least once a day would obviate the 102 rejection. Thus, the response requests withdrawal of the rejection.

This is found unpersuasive because the limitation "about 20 μg/kg at least once a day" (set forth no upper limit for "how many times a day" due to "at least once") broadly but reasonably interpreted as unlimited amount (as along as reasonable amount) of said dose per day. Soltero et al. teaches that dosages can be determined with routine pharmacological procedures known to those skilled in the art, and teaches that the dosage in general is about 0.1 mg/kg (see col.39, lines 28-31). Since instant limitation "…amount is about 20 μg/kg at least once a day (with no upper limit of the amount per day administration) in claims 1-3, the Soltero's teaching as to the dosage meets the instant limitation in this case. Thus, the claim amendment does not obviate the rejection; and therefore, the 102 rejection above is maintained.

[2] (New) Claims 1-3 are rejected under 35 U.S.C. 102(a) or 102(e) as anticipated by Ekwuribe et al. (US 20030060606 A1) which is equivalent to US Pat. No. 6713452, as is evidenced by Yamamoto et al. (US 5059587). For the following rejection 6713452 is cited.

At claims 76-78 and 79-81, Ekwuribe et al. disclose a method of treating a bone disorder in a subject comprising administering to said subject a pharmaceutical composition, wherein the

bone disorder is Paget's disease (patent claims 79 and 81) which is associated with intense pain as is evidenced by Yamamoto et al. (col. 1, lines 64-65). The methods of claims 79 and 81 use the composition disclosed in claims 42 and 47 which are PEGylated sCT at Lys^{11} and Lys^{18}. Since salmon calcitonin (sCT) is unique, the sCT polypeptide inherently reads on instant SEQ ID NO:1. This teaches instant claim 1.

Examiner remark: since dosages can be determined in accordance with routine pharmacological procedures known to those skilled in the art (Col.46, lines 61-63, Ekwuribe et al.), and since instant limitation "about 20 μg/kg at least once a day", as amended on 5/9/1, the upper limit of "how many times a day" (see "at least once") is open, i.e., allowing for unlimited dose administered per day, the above reference's teaching meets the said limitation. Therefore, claim 1 is anticipated. This also applied to the rejection of claims 2 and 3 below.

Patent claim 42 disclose the structural feature of the PEGylate sCT, i.e., the PEGylated sCT molecule comprises a first polyethylene glycol (PEG) moiety covalently coupled to the sCT by a non-hydrolyzable bond, and a second PEG covalently coupled to the first PEG moiety by a hydrolyzable bond, which is identical to that of instant claim 2. Thus, claim 2 is anticipated.

Patent claim 43 (depending from claim 42) disclose the structural feature of the PEGylate sCT identical to that of instant claim 3, i.e., monodispersed mixture of sCT-PEG conjugates containing PEGylation at Lys^{11} and Lys^{18} of sCT wherein said Lys^{11} and Lys^{18} is coupled to at the end distal to the carboxylic acid moiety to a methyl terminated PEG moiety that has at least 7 PEG units,. Thus, instant claim 3 is anticipated.

Claim Rejections - 35 USC §103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

[1] (new) Claim 1 is rejected under 35 U.S.C. 35 U.S.C. 103(a) as unpatentable over as obvious over Lee et al. (US 6506730 B1) in view of Boyd et al. (US Pat. No. 7151191 B2).

Examiner remark: including Boyd et al. reference here is in view of the amendment of claim 1.

In patent claims 1 and 2, Lee et al. teach a method of treatment a disease comprising administering to mammal in need a pharmaceutical composition comprising polyethylene glycol (PEG) conjugated (PEGylated) calcitonin peptide wherein said calcitonin is obtained from Salmon (see Example 1, wherein Salmon calcitonin is termed "sCT"), and wherein the treatment

refers to curing Paget's disease (instantly claimed "Pain" (genus) or "peripheral pain" (genus) encompasses the Paget's disease-caused bone pain) which common symptom is bone pain - a peripheral pain which is resulted from the bone absorption and osteoporosis (see col. 6, line 24-28). The PEGylation occurs at Lys^{11} and Lys^{18} of calcitonin (see col.5, line 54 and Example 4) and teach a "di-PEG-sCT" which is PEG conjugated Lys^{11} and Lys^{18} (see col.5, lines 53-54). Lee et al. teach at pH 8, PEG is increasingly conjugated to Lys^{11} and Lys^{18}, suggesting that under condition at pH 8, majority of "di-PEG-sCT" [Lys^{11} and Lys^{18}] can be obtained. This is because PEGylation of CT is carried out in phosphate buffer, pH 8.0 according to Lee et al. (see Example 1, "*Preparation of PEG-sCT*"). Also, Lee et al. teach a uniformed PEG-peptide conjugate wherein "uniformed" conjugate is equivalent to instant "mono-dispersed mixture conjugate". The sCT is a single chain peptide of 32 amino acids (col.6, lines 23-25). Since calcitonin from a particular species, herein, the species is Salmon, must have unique amino acid sequence, the sCT inherently reads on instant SEQ ID NO:1. These are applied to instant claim 1.

Provided that Lee et al. do not expressly teach use oral administering route and administration dose of sCT about 20 μg/kg at least once a day.

Lee et al. teach that injection administration gives patients pain and has accompanying dangers; and thus, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48), as applied to claims 1-3.

Boyd et al. teach oral delivery of sCT with dose about 30 μg/kg (see col.9, Table 2), and that the dose of active agent to be used can be determined by methods known to those skilled in the art (col.8, lines 11-19), as applied to claim 1.

It would have been obvious to one skilled in the art at the time the invention was made to determine the administration route, e.g., the oral route, and the dose amount of 20 μg/kg at least once a day. This is because the reasons below.

Injection administration gives patients pain and has accompanying dangers; and thus, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48, Lee et al.). Thus, administration route other than injection is sought. Boyd et al. have taught oral delivery for sCT while Lee et al. suggest nasal delivery rout thereof (see abstract). The oral route is considered to be an obvious alternative to nasal route because the oral administration is a convenient and is a preferred route for delivery sCT as taught by Boyd et al. (co.18, lines 41-42); and thus, one of ordinary skill in the art would have tried the oral delivery of sCT.

Boyd et al. have taught useful oral delivery of sCT with dose 30 μg/kg; said dose is considered to be obvious variation of instant 20 μg/kg since the dose of active agent to be used can be determined by methods known to those skilled in the art (col.8, lines 11-19, Boyd et al.). One of ordinary skill in the art thus would have TRIED the oral administration with a proper dose, e.g., about 20 μg/kg per day with reasonable expectation of success in the absence of any unexpected result. Therefore, the combination of references' teachings renders the amended claims 1-3 prima facie obvious.

The applicants' response to the above 103 rejection

At pages 4-7, the response filed 5/9/11 submits that Lee et al. do not teach the di-PEG-sCT" wherein PEG polymers are conjugated Lys^{11} and Lys^{18} at Example 4 and discusses Fig. 2 in this regard (p.5, 1st paragraph). The response argues that Lee et al. only teach nasal transmucosal administration not oral delivery of the composition on the amount of about 20 μg/kg at least once a day (p.5, 2nd paragraph), and that Lee discourage the use of oral route and thus one of skilled in the art would never consider oral administration just because the injection

is painful, and because Lee et al. discusses negative side effect of oral administration (p.5, last paragraph to p.6, paragraph 3). Thus, the response infers that a prima facie case of obviousness is not established and requests withdrawal of the rejection.

The applicants' arguments are found unpersuasive because of the reasons set forth in the rejection and the reasons below.

Lee et al. have taught the di-PEG-sCT (Example 4) wherein PEG polymers are conjugated to Lys^{11} and Lys^{18} of sCT, and have taught PEGylation at pH 8; under PEGylation reaction condition at said pH 8, said di-PEG-sCT can be obtained (see above corresponding discussion).

As far as the oral route is concerned, although Lee et al. discuses some advantage of nasal delivery over oral administration route, the oral route is considered to be an obvious alternative to nasal route because the oral administration is not only a convenient route but also is a preferred route for delivery sCT as taught by Boyd et al. (co.18, lines 41-42). Lee et al. have taught that due to pain and accompanying dangers, injection is not preferred and thus there remains a need to develop other routes for peptide administration (col.1, lines 43-48). By seeking said other route, the oral route is such choice for administering the peptide drug PEGylated sCT, and therefore, it would have be obvious for one of ordinary skill in the to try said oral delivery of the peptide drug. As discussed above, Boyd et al. have taught useful oral delivery of sCT with dose 30 μg/kg; said dose is considered to be obvious variation of instant 20 μg/kg; this is because the dose of active agent to be used can be determined by methods known to those skilled in the art as taught by Boyd et al. (col.8, lines 11-19). One of ordinary skill in the art thus would have TRIED the oral administration with a proper dose, e.g., about 20 μg/kg per day with reasonable expectation of success in the absence of any unexpected result. Therefore, the combination of references' teachings renders the amended claim 1 prima facie obvious.

[2] (new) Claim 1 is rejected under 35 U.S.C. 103(a) as unpatentable over as obvious over Russo A. F. (US Pat. No. 5976788) in view of Komarova et al. (*Calcif. Tissue Int.* (2003, online published 6/6/03) 73, 265-273), and Boyd et al. (US Pat. No. 7151191 B2).

Examiner remark: including Boyd et al. reference here is in view of the amendment of claim 1.

Russo teaches that calcitonin (CT) has therapeutic application for relieve pain such as "hypercalcemia pain" (see col. 9, lines 18-21). This suggests use of sCT to treat pain. Yet, Russo does not expressly teach use PEGylated CT for treating pain, e.g., hypercalcemia pain, wherein PEGylation includes PEGylation at Lys^{11} and Lys^{18} residues of CT (claim1), nor expressly teach oral administering route.

Komarova et al. teach PEGylation of Salmon calcitonin (sCT) peptide (Fig. 1) at Lys^{11} and Lys^{18} residues and teach advantages of the PEGylation of enhance stability, increases half-life and decrease immunogenicity of said sCT peptide (see p.265, right col., 2nd paragraph, and Fig. 1), wherein the amino acid sequence depicted in Fig.1 has 100% sequence identity to instant SEQ ID NO:1, as applicable to claim 1.

Provided that Russo and Komarova et al. do not expressly teach oral administration route with dose of sCT about 20 μg/kg at least once a day for treating pain.

Boyd et al. teach oral delivery of sCT with dose about 30 μg/kg (see Example 2, Table 2 at col.19), and that the dose of active agent to be used can be determined by methods known to those skilled in the art (col.8, lines 11-19), as applied to claim 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the PEGylated sCT for treating the pain condition, wherein the PEG moiety is conjugated to the sCT peptide directly through amino acids Lys^{11} and Lys^{18}. This is because Russo has taught usefulness of sCT peptide for treating pain, and becasue Komarova et al. have taught that the sCT peptide is PEGylated at of Lys^{11} and Lys^{18} side chains. This PEGylation has advantage over the unpegylated peptide thereof in enhanced stability, increases half-life and decreased immunogenicity (see above). Thus, it would have been obvious for one of ordinary

skill in the art to substitute the PEGylated sCT for the non-PEGylated sCT for treating pain in a subject in need thereof with reasonable expectation of success.

Considering the administering route for delivery of sCT for the pain treatment, Boyd et al. have taught useful oral delivery of sCT with dose 30 μg/kg (see Example 2, Table 2); said dose is considered to be an obvious variation of instant 20 μg/kg, since the dose of active agent to be used can be determined by methods known to those skilled in the art as taught by Boyd et al. (col.8, lines 11-19). Thus, one of ordinary skill in the art thus would have TRIED the oral administration with a proper dose, e.g., about 20 μg/kg per day to treat pain in the subject with reasonable expectation of success in the absence of any unexpected result. Therefore, the combination of references' teachings renders the amended claim 1 prima facie obvious.

The applicants' response to the above 103 rejection

At page 7, the response filed 5/9/11 argues that Russo does not teach use of PEGylated CT (PEG is conjugated at Lys^{11} and Lys^{18} in CT polypeptide), whereas Komarova et al. only teach use of the PEGylated CT in vitro testing on HEK293 cells, and both references Russo and Komarova do not teach the dose of 20 μg/kg at least once a day. Thus, the response requests withdrawal of the rejection.

The applicants' arguments are found unpersuasive because of the reasons set forth in the rejection and the reasons below.

Russo has taught usefulness of sCT to treating pain, Komarova et al. have taught that the PEGylated sCT is advantageous over unpegylated sCT in enhanced stability, increases half-life and decreased immunogenicity, wherein PEGylation is at Lys^{11} and Lys^{18} of said sCT polypeptide side chains. The applicants' assertion "in vitro testing on HEK293 cells" is not at issue in this regard. These advantages would have motivated one of ordinary skill in the art to try use of said PEGylated sCT [Lys^{11} and Lys^{18}] to treat pain with reasonable expectation of success.

The oral route is considered to be an obvious alternative to nasal route. This is because the oral administration is not only a convenient route but also is a preferred route for delivery sCT as taught by Boyd et al. (co.18, lines 41-42), and because Boyd et al. have explicitly taught

and provided working example (see Example 2, Table 2) for oral delivery of sCT with dose 30 μg/kg which is considered to be an obvious variation of instant 20 μg/kg; this is because determination of the dose of active agent to be used in the treatment is well within the purview of those skilled in the art as taught by Boyd et al. (col.8, lines 11-19). One of ordinary skill in the art thus would have TRIED the oral administration with a proper dose, e.g., about 20 μg/kg per day in the absence of any unexpected result. Therefore, the combination of references' teachings renders the amended claim 1 prima facie obvious, and therefore, the 103 rejection stands.

[3] (new) Claim 2 is rejected under 35 U.S.C. 103(a) as unpatentable over as obvious over Russo A. F. (US Pat. No. 5976788) in view of Komarova et al. (*Calcif. Tissue Int.* (2003, online published on 6/6/03) 73, 265-273), Ekwuribe et al. (US 2003/0060606 A1), and Boyd et al. (US Pat. No. 7151191 B2).

Russo teaches that calcitonin (**CT**) has therapeutic application for relieve pain such as "hypercalcemia pain" (see col. 9, lines 18-21).

Komarova et al. teach PEGylation of Salmon calcitonin (sCT) peptide (Fig. 1) and the advantages of the PEGylation: enhance stability, increases half-life and decrease immunogenicity of said CT peptide, wherein PEGylation occurs at Lys^{11} and Lys^{18} side chains of the sCT peptide (see p.265, right col., 2nd paragraph, and Fig. 1), wherein the amino acid sequence depicted in Fig.1 has 100% sequence identity to instant SEQ ID NO:1. The Russo and Komarova teachings are applied to claim 2.

Provided that Russo and Komarova et al. do not expressly teach attachment of a non-hydrolysable linker between the peptide PEGylated and polyethylene glycol (PEG) nor expressly teach oral administration with a dose of 20 μg/kg at least once a day for treating pain.

Ekwuribe et al. teach the PEGylated salmon calcitonin (sCT) oligomer (wherein one PEG is coupled to Lys^{11} and other PEG to Lys^{18} (see PGPUB claim 15) that comprises a first

polyethylene glycol (PEG) moiety covalently coupled to the sCT by a non-hydrolyzable bond, and a second PEG covalently coupled to the first PEG moiety by a hydrolyzable bond (see PGPUB claim 24, [0095], [0142], [0119] and [0176]). Further, Ekwuribe et al. teach that the hydrolyzable coupling provides a calcitonin drug-oligomer conjugate that acts as a prodrug which allows for a time-release or controlled-release of sCT (see [0093], lines 41-14) while the non-hydrolyzable bond is preferable when it is desirable to allow the sCT drug conjugate to circulate in the bloodstream for an extended period of time, preferably at least 2 hours (see [0093], lines 14-20), as applied to claim 2.

Boyd et al. teach oral delivery of sCT with dose about 30 μg/kg (see Example 2, Table 2 at col.19), and that the dose of active agent to be used can be determined by methods known to those skilled in the art (col.8, lines 11-19), as applied to claim 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to introduce a hydrolysable linker or bond between the peptide and PEG moiety. This is because Russo has taught usefulness of sCT peptide for treating pain, and Komarova et al. have taught that the PEGylated [Lys^{11} and Lys^{18}] sCT peptide is advantageous over the unpegylated peptide at least in three aspects: enhanced stability, increases half-life and, and decreased immunogenicity. By taking these advantages, it would have been obvious to use the PEGylated [Lys^{11} and Lys^{18}] sCT as taught by Komarvoa for treating or relieving pain as taught by Russo.

Ekwuribe et al. have taught the same PEGylated [Lys^{11} and Lys^{18}] as Komarova et al. have disclosed, and have taught the advantages of use of the "non-hydrolysable bod and hydrolysable bond, i.e., (i) a first PEG covalently coupled to the CT by a non-hydrolyzable bond, and (ii) a second PEG moiety covalently coupled to said first PEG a hydrolyzable bond with the

following advantages that (A) the hydrolyzable bond (coupling) allows sCT actin as thereby render a time-release or controlled-release of sCT feasible; and (B) while the non-hydrolyzable bond is desirable to allow the CT drug conjugate to circulate in the bloodstream for an extended period of time, i.e., increased $t_{1/2}$ (see above corresponding discussion). Thus, it would have been obvious to apply the non-hydrolyzable and hydrolyzable coupling (bond) to the PEGylation of sCT for treating pain.

As far as the oral route with the dose of "20 μg/kg at least once a day" is concerned, the oral route is considered to be an obvious alternative to nasal route. This is because the oral administration is not only a convenient route but also is a preferred route for delivery sCT as taught by Boyd et al. (co.18, lines 41-42), and because Boyd et al. have explicitly taught and provided working example (see Example 2, Table 2) for oral delivery of sCT with dose 30 μg/kg which is considered to be an obvious variation of instant 20 μg/kg, since determination of the dose of active agent to be used in the treatment is well within the purview of those skilled in the art as taught by Boyd et al. (col.8, lines 11-19). One of ordinary skill in the art thus would have TRIED the oral administration with a proper dose, e.g., about 20 μg/kg per day in the absence of any unexpected result. Therefore, the combination of references' teachings renders the amended claim 2 prima facie obvious.

The applicants' response to the above 103 rejection

At page 7, the response filed 5/9/11 argues that Russo does not teach use of PEGylated sCT (PEG is conjugated at Lys^{11} and Lys^{18} in sCT polypeptide), whereas Komarova et al. only teach use of the PEGylated sCT in vitro testing on HEK293 cells. These two references never teach the oral dose of 20 μg/kg at least once a day. Based on the arguments, the response requests withdrawal of the rejection.

The applicants' arguments are found unpersuasive because of the reasons set forth in the rejection and the reasons below. Russo has taught usefulness of sCT to treating pain, Komarova et al. have taught that the PEGylated sCT is advantageous over unpegylated sCT in enhanced stability, increases half-life and decreased immunogenicity, wherein PEGylation is at Lys^{11} and Lys^{18} of said sCT polypeptide side chains. The applicants assertion "in vitro testing on HEK293 cells" is not at issue in this regard. The advantages taught by Komarova et al. would have motivated one of ordinary skill in the art to try use of said PEGylated [Lys^{11} and Lys^{18}] sCT to treat pain. The oral route is considered to be an obvious alternative to nasal route. This is because the oral administration is not only a convenient route but also is a preferred route for delivery sCT as taught by Boyd et al. (co.18, lines 41-42) [currently cited], and because Boyd et al. have taught and provided working example (see Example 2, Table 2) for oral delivery of sCT with dose 30 μg/kg which is considered to be an obvious variation of instant 20 μg/kg; this is because determination of the dose of active agent to be used in the treatment is well within the purview of those skilled in the art as taught by Boyd et al. (col.8, lines 11-19). One of ordinary skill in the art thus would have TRIED the oral administration with a proper dose, e.g., about 20 μg/kg per day in the absence of any unexpected result. Further in view of the Ekwuribe et al. (newly cited0 teaching regarding PEGylated [Lys^{11} and Lys^{18}] sCT with the non-hydrolyzable and the hydrolyzable (see above), the combination of the above 103 references' teachings renders the amended claim 2 obvious. Therefore, the 103 rejection stands.

[4] (new) Claim 3 is rejected under 35 U.S.C. 103(a) as unpatentable over as obvious over Russo A. F. (US Pat. No. 5976788) in view of Komarova et al. (*Calcif. Tissue Int.* (2003, online published on 6/6/03) 73, 265-273), Boyd et al. (US Pat. No. 7151191 B2), Crotts et al. (US 2003/0017203 A1), and Ekwuribe et al. (US 2003/0060606 A1).

Russo teaches that CT therapeutic use in relieving pain, e.g., "hypercalcemia pain" and treating Paget's disease (col. 9, lines 17-21).

Komarova et al. teach PEGylation of Salmon calcitonin (sCT) peptide (Fig. 1) and the advantages of the PEGylation: enhance stability, increases half-life and decrease immunogenicity of said CT peptide, wherein PEGylation occurs at Lys^{11} and Lys^{18} side chains of

the sCT peptide (see p.265, right col., 2nd paragraph, and Fig. 1), wherein the amino acid sequence depicted in Fig.1 has 100% sequence identity to instant SEQ ID NO:1.

These are applied to claim 3.

Provided that Russo and Komarova et al. and do not expressly teach attachment of a carboxylic acid as a linker between the peptide and PEG, nor teach oral administration with a dose of 20 μg/kg at least once a day for treating pain.

Ekwuribe et al. disclose the PEGylated [Lys^{11} and Lys^{18}] sCT, and disclose a monodispersed mixture of sCT-PEG conjugates containing PEGylation at Lys^{11} and Lys^{18} of sCT wherein said Lys^{11} and Lys^{18} is coupled to at the end distal to the carboxylic acid moiety to a methyl terminated PEG moiety that has at least 7 PEG units (see PGPUB claims 28-29, [0013], [0038], [0110], and Fig.4); this teaches the corresponding structural limitation in claim 3.

Further, Boyd et al. teach oral delivery of sCT with a dose about 30 μg/kg (see Example 2, Table 2 at col.19), and that the dose of active agent to be used can be determined by methods known to those skilled in the art (col.8, lines 11-19), as applied to claim 3.

Crotts et al. teach that sCT is biologically difficult to penetrate the mucus membranes which limits its bioavailability (see [0004], lines 11-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to introduce a hydrolysable linker or bond between the peptide and PEG moiety. This is because Russo has taught usefulness of sCT peptide for treating pain, and Komarova et al. have taught that the PEGylated [Lys^{11} and Lys^{18}] sCT peptide is advantageous over the unpegylated peptide at least in three aspects: enhanced stability, increases half-life and, and

decreased immunogenicity. By taking these advantages, it would have been obvious to use the PEGylated [Lys^{11} and Lys^{18}] sCT as taught by Komarvoa to treat/relieve pain as taught by Russo.

As far as the attachment of carboxylic acid to sCT-PEG conjugate is concerned, Ekwuribe et al. have taught incorporation of a carboxylic acid such as "octanoic acid" (an eight-carbon saturated fatty acid (see col. 13, line 6) into between PEG moiety and the sCT peptide PEGylated (see the above teaching as to "*Lys^{11} and Lys^{18} is coupled to at the end distal to the carboxylic acid moiety to a methyl terminated PEG moiety that has at least 7 PEG units*" at PGPUB claims 28-29, especially). Like Komarova et al., the Ekwuribe' PEGylated product is also directed to use of the PEGylated [Lys^{11} and Lys^{18}] sCT. This is the nexus between the teachings of Russo and Komarova et al. and teaching of Ekwuribe et al. herein. In the relative field, it has been known that sCT has a biologically difficult (problem) to penetrate the mucus membranes which limits its bioavailability (see [0004], lines 11-15, Crotts) and thereby its clinical use. Upon reading the Ekwuribe's reference as to the PEG-sCT conjugate containing linked carboxylic acid moiety, e.g., octanoic acid (see [0013], line 6, Ekwuribe et al.) an eight eight-carbon saturated fatty acid and together upon reading Crotts' reference, one of ordinary skill in the art would have readily realized said penetration problem of sCT can be resolved by using fatty acid-linked PEG-sCT conjugate taught by Ekwuribe et al. because of ability of fatty acid acting as membrane penetration enhancer, thereby improve sCT therapeutic use such as treating pain

As far as the oral route with the dose of "20 μg/kg at least once a day" is concerned, the oral route is considered to be an obvious alternative to nasal route. This is because the oral administration is not only a convenient route but also is a preferred route for delivery sCT as

taught by Boyd et al. (co.18, lines 41-42), and because Boyd et al. have explicitly taught and provided working example (see Example 2, Table 2) for oral delivery of sCT with dose 30 μg/kg which is considered to be an obvious variation of instant 20 μg/kg, since determination of dose of active agent to be used in the treatment is well within the purview of those skilled in the art as taught by Boyd et al. (col.8, lines 11-19). One of ordinary skill in the art thus would have TRIED the oral administration with a proper dose, e.g., about 20 μg/kg per day in the absence of any unexpected result. Therefore, the combination of references' teachings renders the amended claim 2 prima facie obvious.

As far as the administration route and the dose are concerned, Boyd et al. have taught oral delivery of sCT with dose about 30 μg/kg, and have taught that the dose of active agent to be used can be determined by methods known to those skilled in the art (col.8, lines 11-19); and thus, the Boyd' dose is considered to be an obvious variation instant "20 μg/kg at least once a day". One of ordinary skill in the art, thus, would have TRIED the oral administration with a proper dose, e.g., about 20 μg/kg per day in the absence of any unexpected result. Therefore, the combination of references' teachings renders claim 3 prima facie obvious.

The applicants' response to the 103 rejections

At page 8, the response filed 5/9/11 argues that Russo does not teach use of PEGylated sCT (PEG is conjugated at Lys^{11} and Lys^{18} in sCT polypeptide), whereas Komarova et al. only teach use of the PEGylated CT in vitro testing on HEK293 cells. These two references never teach the oral dose of 20 μg/kg at least once a day. The response asserts that Crotts et al. does not overcome the shortcomings of the Komarova and Russo, and thus, the response requests withdrawal of the rejection.

The applicants' arguments are found unpersuasive because Russo has taught usefulness of sCT to treating pain, Komarova et al. have taught that the PEGylated [Lys^{11} and Lys^{18}] sCT is advantageous over unpegylated sCT in enhanced stability, increases half-life and decreased

immunogenicity. Said advantages would render the claim obvious over the combination of Russo and Komarova teachings. The applicants' assertion "in vitro testing on HEK293 cells" is not at issue in this regard.

Crotts et al. discusses the issue reagrding that the sCT membrane penetration need to be improved with respect to its bioavailability thereby its therapeutic effectiveness because the sCT must be penetrate through biomembrane of the target tissues/cells to have its therapeutic role such as treating pain.

As discussed above, the combination of 103 references' teachings has established prima facie case of obviousness. Thus, the 103 rejection stands.

Claim Rejection -Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

CLAIM INTERPRETATION: the limitation "about 20 μg/kg at least once a day", as amended on 5/9/1, (set forth no upper limit for "how many times a day" due to "at least once") is broadly but reasonably interpreted as unlimited amount (as along as reasonable amount) of said dose per day. Thus, the following rejection is applicable.

Claims 1-3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23, 34, 42, 47 70-73 and 76-78 of US Pat. No.

6713452 ('452) although the conflicting claims are not identical, they are not patentable distinct from each other because of the following reasons.

Claims 23, 34, 42, 43, 47 70-73 and 76-81 of '452 disclose a method of treating a bone disorder in a subject wherein the bone disorder is Paget's disease (patent claim 72) which is associated with intense pain in some stage (see col. 1, lines 39-51, '452 specification) comprising oral (see Example 52) administering PEGylated salmon calcitonin (sCT) wherein the calcitonin peptide is PEGylated at lysine residues 11 and 18 (claim 1 of '452), which disclose common subject matter of instant claim 1.

Claims 42 and 43 of '452 disclose the same structural feature of the PEGylated sCT as instant claim 3, and thus, the method of treating Paget's disease (associated with pain) in claims 76-78 which use the product of claims 42 and 43 discloses the common subject matter of claim 3.

Claim 23 of '452 discloses the same structural feature of the PEGylated sCT as instant claim 2, and thus, the method of treating Paget's disease (associated with pain) in claims 70-73 which use the product of claim 23 discloses the common subject matter of claim 3.

Page 8 of the response filed 5/9/11 requests abeyance of the obvious-type double patenting rejection until allowable subject matter is indicated. Note that no allowable subject matter can be indicated with a standing ground of rejection. Thus, it is suggested that applicant file the appropriate terminal disclaimer. It is also note that this ODP rejection was a similarly addressed in the Office action mailed 4/22/10 and discussed in page 2 of the Office action mailed 12/28/10.

Conclusion

No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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